

What is claimed is:

1. A method of determining disease status of a patient suffering from a disease characterized by aberrant expression of one or more ErbB cell surface receptor complexes, the method comprising the steps of:
  - measuring directly in a patient sample an amount of each of one or more ErbB cell surface receptor complexes;
  - comparing each such amount to its corresponding amount in a reference sample; and
  - correlating differences in the amounts from the patient sample and the respective corresponding amounts from the reference sample to the disease status the patient.
2. The method of claim 1 wherein said disease is a cancer and wherein said patient sample is a fixed tissue sample, a frozen tissue sample, or circulating epithelial cells.
3. The method of claim 2 wherein said one or more ErbB cell surface receptor complexes are selected from the group consisting of Her1-Her1 homodimers, Her2-Her2 homodimers, Her1-Her3 receptor dimers, Her2-Her4 receptor dimers, Her1-PI3K complexes, Her2-PI3K complexes, Her3-PI3K complexes, Her1-SHC complexes, Her2-SHC complexes, Her3-SHC complexes, Her1-IGF-1R receptor dimers, Her2-IGF-1R receptor dimers, Her3-IGF-1R receptor dimers, Her1-PDGFR receptor dimers, Her2-PDGFR receptor dimers, Her3-PDGFR receptor dimers, p95Her2-Her3 receptor dimers, p95Her2-Her2 receptor dimers, p95Her2-Her1 receptor dimers, EGFRvIII-Her1 receptor dimers, EGFRvIII-Her2 receptor dimers, and EGFRvIII-Her3 receptor dimers.
4. The method of claim 3 wherein each of said one or more ErbB cell surface receptor complexes are determined by the steps of:
  - providing for each of said one or more Her complexes a reagent pair comprising a cleaving probe having a cleavage-inducing moiety with an effective proximity, and one or more binding compounds each having one or more molecular tags attached thereto by a cleavable linkage, the molecular tags of different binding compounds having different separation characteristics;
  - mixing the cleaving probe and the one or more binding compounds for each of said one or more Her complexes with said patient sample such that the cleaving probe and the one or more binding compounds specifically bind to their respective Her complexes and the cleavable linkages of the one or more binding compounds are within the effective proximity of the cleavage-inducing moiety so that molecular tags are released; and

separating and identifying the released molecular tags to determine the presence or absence or the amount of said one or more ErbB cell surface receptor complexes in said patient sample.

5        5.        The method of claim 4 wherein said patient sample is said fixed tissue sample or said frozen tissue sample.

6.        The method according to claims 3, 4, or 5 wherein said disease status is responsiveness of said patient to treatment with a dimer-acting drug.

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7.        The method of claim 6 wherein said cancer is selected from the group consisting of breast cancer, ovarian cancer, prostate cancer, and colorectal cancer.

8.        The method of claim 1 wherein said one or more ErbB cell surface receptor complexes  
15 are one or more heterodimers with a PDGF receptor.

9.        The method of claim 8 wherein said one or more heterodimers are selected from the group consisting of Her1-PDGFR receptor dimers, Her2-PDGFR receptor dimers, and Her3-PDGFR receptor dimers.

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10.       The method of claim 9 wherein said patient sample is said fixed tissue sample or said frozen tissue sample.

11.       The method of claim 10 wherein said one or more heterodimers are determined by the  
25 steps of:

providing for each of said one or more heterodimers a reagent pair comprising a cleaving probe having a cleavage-inducing moiety with an effective proximity, and one or more binding compounds each having one or more molecular tags attached thereto by a cleavable linkage, the molecular tags of different binding compounds having different separation characteristics;

30        mixing the cleaving probe and the one or more binding compounds for each of said one or more heterodimers with said patient sample such that the cleaving probe and the one or more binding compounds specifically bind to their respective heterodimers and the cleavable linkages of the one or more binding compounds are within the effective proximity of the cleavage-inducing moiety so that molecular tags are released; and

35        separating and identifying the released molecular tags to determine the presence or absence or the amount of said one or more heterodimers in said patient sample.

12. The method according to claims 8, 9, 10, or 11 wherein said disease is cancer or wherein said disease is associated with an aberrant fibrotic condition.
13. The method of claim 12 wherein said cancer is selected from the group consisting of breast cancer, ovarian cancer, and glioblastoma.
14. The method of claim 1 wherein said patient sample is a fixed tissue sample and wherein said disease is cancer and wherein said one or more ErbB cell surface receptor complexes are Her receptor dimers selected from the group consisting of Her1-Her1, Her1-Her3, Her1-Her4, Her2-Her2, Her3-Her4, and Her4-Her4.
15. The method of claim 14 wherein said one or more Her receptor dimers are determined by the steps of:
- providing for each of said one or more Her receptor dimers a reagent pair comprising a cleaving probe having a cleavage-inducing moiety with an effective proximity, and one or more binding compounds each having one or more molecular tags attached thereto by a cleavable linkage, the molecular tags of different binding compounds having different separation characteristics;
  - mixing the cleaving probe and the one or more binding compounds for each of said one or more Her receptor dimers with said patient sample such that the cleaving probe and the one or more binding compounds specifically bind to their respective Her receptor dimers and the cleavable linkages of the one or more binding compounds are within the effective proximity of the cleavage-inducing moiety so that molecular tags are released; and
  - separating and identifying the released molecular tags to determine the presence or absence or the amount of said one or more Her receptor dimers in said fixed tissue sample.
16. A method of selecting a patient for treatment of a cancer with one or more ErbB-dimer-acting drugs, the method comprising the steps of:
- isolating a patient sample containing cancer cells from a patient;
  - measuring directly in the patient sample an amount of each of one or more ErbB cell surface receptor dimers;
  - comparing each such amount to its corresponding amount from a reference sample; and
  - selecting the patient for treatment with one or more ErbB dimer-acting drugs whenever an amount of one or more cell surface receptor dimers from the patient sample exceeds the respective corresponding amount from the reference sample.

17. The method of claim 16 wherein said patient sample is a fixed tissue sample, a frozen tissue sample, or circulating epithelial cells.
18. The method of claim 17 wherein said ErbB cell surface receptor dimer contains a Her1  
5 receptor and said dimer-acting drug is selected from the group consisting of Cetuximab (Erbix), Trastuzumab (Herceptin), h-R3 (TheraCIM), ABX-EGF, MDX-447, ZD-1839 (Iressa), OSI-774 (Tarceva), PKI 166, GW572016, CI-1033, EKB-569, and EMD 72000.
19. The method of claim 18 wherein said ErbB cell surface receptor dimer is selected from  
10 the group consisting of Her1-Her1, Her1-Her2, Her1-Her3, Her1-Her4.
20. The method of claim 19 wherein said ErbB cell surface receptor dimer is selected from the group consisting of Her1-Her1, Her1-Her3, Her1-Her4.
21. The method of claim 20 wherein said ErbB cell surface receptor dimer is Her1-Her1.
22. The method of claim 21 wherein said patient sample is a fixed tissue sample and wherein said ErbB dimer-acting drug selected from the group consisting of Cetuximab (Erbix), ABX-EGF, MDX-447, ZD-1839 (Iressa), OSI-774 (Tarceva), PKI 166, GW572016, CI-1033, EKB-  
20 569, and EMD 72000.
23. The method according to claims 16, 17, 18, 19, 20, 21, or 22 wherein said one or more ErbB cell surface receptor dimers are determined by the steps of:
- 25 providing for each of said one or more ErbB cell surface receptor dimers a reagent pair comprising a cleaving probe having a cleavage-inducing moiety with an effective proximity, and one or more binding compounds each having one or more molecular tags attached thereto by a cleavable linkage, the molecular tags of different binding compounds having different separation characteristics;
- 30 mixing the cleaving probe and the one or more binding compounds for each of said one or more ErbB cell surface receptor dimers with said patient sample such that the cleaving probe and the one or more binding compounds specifically bind to their respective ErbB cell surface receptor dimers and the cleavable linkages of the one or more binding compounds are within the effective proximity of the cleavage-inducing moiety so that molecular tags are released; and

separating and identifying the released molecular tags to determine the presence or absence or the amount of said one or more ErbB cell surface receptor dimers in said fixed tissue sample.

- 5     24.     A method of determining a cancer status of a patient suffering from a cancer characterized by aberrant expression of one or more ErbB cell surface receptor complexes, the method comprising the steps of:

measuring directly in a patient sample an amount of each of one or more ErbB cell surface receptor complexes;

- 10         comparing each such amount to its corresponding amount in a reference sample; and  
correlating differences in the amounts from the patient sample and the respective corresponding amounts from the reference sample to the disease status the patient;

wherein said one or more ErbB cell surface receptor complexes are selected from the group consisting of Her1-PI3K complexes, Her2-PI3K complexes, Her3-PI3K complexes, Her1-SHC complexes, Her2-SHC complexes, Her3-SHC complexes, Her1-IGF-1R receptor dimers, Her2-IGF-1R receptor dimers, Her3-IGF-1R receptor dimers, Her1-PDGFR receptor dimers, Her2-PDGFR receptor dimers, Her3-PDGFR receptor dimers, p95Her2-Her3 receptor dimers, p95Her2-Her2 receptor dimers, p95Her2-Her1 receptor dimers, EGFRvIII-Her1 receptor dimers, EGFRvIII-Her2 receptor dimers, and EGFRvIII-Her3 receptor dimers.

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25.     The method of claim 24 wherein said disease is a cancer and wherein said patient sample is a fixed tissue sample, a frozen tissue sample, or circulating epithelial cells.

26.     The method of claim 25 wherein each of said one or more ErbB cell surface receptor  
25     complexes are determined by the steps of:

providing for each of said one or more ErbB cell surface receptor complexes a reagent pair comprising a cleaving probe having a cleavage-inducing moiety with an effective proximity, and one or more binding compounds each having one or more molecular tags attached thereto by a cleavable linkage, the molecular tags of different binding compounds having different  
30     separation characteristics;

mixing the cleaving probe and the one or more binding compounds for each of said one or more ErbB cell surface receptor complexes with said patient sample such that the cleaving probe and the one or more binding compounds specifically bind to their respective ErbB cell surface receptor complexes and the cleavable linkages of the one or more binding compounds are  
35     within the effective proximity of the cleavage-inducing moiety so that molecular tags are released; and

separating and identifying the released molecular tags to determine the presence or absence or the amount of said one or more ErbB cell surface receptor complexes in said patient sample.

5     27.     The method of claim 26 wherein said patient sample is said fixed tissue sample or said frozen tissue sample.

28.     The method according to claims 24, 25, 26, or 27 wherein said cancer status is responsiveness of said patient to treatment with a dimer-acting drug.

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29.     The method of claim 28 wherein said cancer is selected from the group consisting of breast cancer, ovarian cancer, prostate cancer, and colorectal cancer.

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30.     A method of determining disease status of a patient suffering from a disease characterized by aberrant expression of one or more ErbB cell surface receptor complexes, the method comprising the steps of:

measuring directly in a patient sample an amount of each of one or more ErbB cell surface receptor complexes;

comparing each such amount to its corresponding amount in a reference sample;

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correlating differences in the amounts from the patient sample and the respective corresponding amounts from the reference sample to the disease status the patient; and

wherein each of said one or more ErbB cell surface receptor complexes are determined by the steps of:

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providing for each of said one or more ErbB cell surface receptor complexes and one or more tissue indicators a reagent pair comprising a cleaving probe having a cleavage-inducing moiety with an effective proximity, and one or more binding compounds each having one or more molecular tags attached thereto by a cleavable linkage, the molecular tags of different binding compounds having different separation characteristics;

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mixing the cleaving probe and the one or more binding compounds for each of said one or more ErbB cell surface receptor complexes and one or more tissue indicators with said patient sample such that the cleaving probe and the one or more binding compounds specifically bind to their respective targets and the cleavable linkages of the one or more binding compounds are within the effective proximity of the cleavage-inducing moiety so that molecular tags are released; and

separating and identifying the released molecular tags to determine the presence or absence or the amount of said one or more ErbB cell surface receptor complexes in said patient sample.

5     31.     The method of claim 30 wherein said disease is a cancer and wherein said patient sample is a fixed tissue sample, a frozen tissue sample, or circulating epithelial cells.

32.     The method of claim 31 wherein said disease status is responsiveness of said patient to treatment with a dimer-acting drug.

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33.     The method of claim 31 wherein said cancer is selected from the group consisting of breast cancer, ovarian cancer, prostate cancer, and colorectal cancer.

34.     The method of claim 31 wherein said one or more ErbB cell surface receptor complexes  
15     are selected from the group consisting of Her1-Her1 homodimers, Her2-Her2 homodimers, Her1-Her3 receptor dimers, Her2-Her4 receptor dimers, Her1-PI3K complexes, Her2-PI3K complexes, Her3-PI3K complexes, Her1-SHC complexes, Her2-SHC complexes, Her3-SHC complexes, Her1-IGF-1R receptor dimers, Her2-IGF-1R receptor dimers, Her3-IGF-1R receptor dimers, Her1-PDGFR receptor dimers, Her2-PDGFR receptor dimers, Her3-PDGFR receptor dimers,  
20     p95Her2-Her2 receptor dimers, EGFRvIII-Her1 receptor dimers, and EGFRvIII-Her3 receptor dimers.

35     The method of claim 34 wherein said one or more ErbB cell surface receptor complexes are selected from the group consisting of Her1-Her1 homodimers.

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36.     The method of claim 31 wherein said one or more ErbB cell surface receptor complexes each at least one Her2 receptor and at least one of either PI3K or SHC.

37.     The method of claim 31 wherein said cancer is selected from the group consisting of  
30     breast cancer, ovarian cancer, prostate cancer, and colorectal cancer.

38.     The method of claim 31 wherein said patient sample is said fixed tissue sample or said frozen tissue sample.

39. A method of determining a cancer status of a patient suffering from a cancer characterized by aberrant expression of one or more ErbB cell surface receptor complexes, the method comprising the steps of:
- measuring directly in a patient sample an amount of each of one or more ErbB cell surface receptor complexes;
- comparing each such amount to its corresponding amount in a reference sample;
- correlating differences in the amounts from the patient sample and the respective corresponding amounts from the reference sample to the disease status the patient; and
- wherein said one or more ErbB cell surface receptor complexes each comprise a Her receptor and an intracellular adaptor molecule.
40. The method of claim 1 wherein said patient sample is a fixed tissue sample, a frozen tissue sample, or circulating epithelial cells.
41. The method of claim 40 wherein each of said one or more ErbB cell surface receptor complexes are determined by the steps of:
- providing for each of said one or more ErbB cell surface receptor complexes a reagent pair comprising a cleaving probe having a cleavage-inducing moiety with an effective proximity, and one or more binding compounds each having one or more molecular tags attached thereto by a cleavable linkage, the molecular tags of different binding compounds having different separation characteristics;
- mixing the cleaving probe and the one or more binding compounds for each of said one or more ErbB cell surface receptor complexes with said patient sample such that the cleaving probe and the one or more binding compounds specifically bind to their respective ErbB cell surface receptor complexes and the cleavable linkages of the one or more binding compounds are within the effective proximity of the cleavage-inducing moiety so that molecular tags are released; and
- separating and identifying the released molecular tags to determine the presence or absence or the amount of said one or more ErbB cell surface receptor complexes in said patient sample.
42. The method of claim 41 wherein said patient sample is said fixed tissue sample or said frozen tissue sample.
43. The method of claim 42 wherein said cancer is selected from the group consisting of breast cancer, ovarian cancer, prostate cancer, and colorectal cancer.



44. The method according to claims 39, 40, 41, 42, or 43 wherein said one or more ErbB cell surface receptor complexes include one or more complexes selected from the group consisting of Her1-PI3K complexes, Her2-PI3K complexes, Her3-PI3K complexes, Her1-SHC  
5 complexes, Her2-SHC complexes, Her3-SHC complexes, IGF-1R-PI3K complexes, IGF-1R-SHC complexes, PDGFR-PI3K complexes, and PDGFR-SHC complexes.

45. The method according to claim 44 wherein said cancer status is responsiveness of said patient to treatment with a dimer-acting drug.

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